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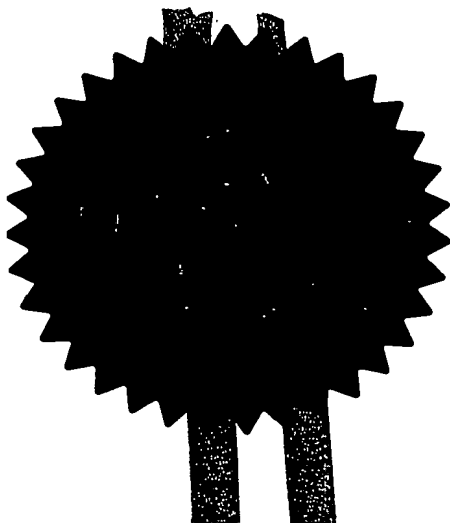
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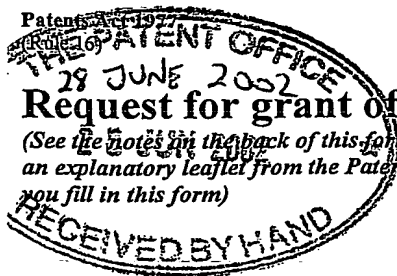


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1. Your reference

MJN/LP6056568

2. Patent application number

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Patents ADP number (if you know it)

SCIONA LIMITED
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If the applicant is a corporate body, give the country/state of its incorporation

08414625001

ENGLAND

4. Title of the invention

SAMPLING KITS, DEVICES AND USES THEREOF

5. Name of your agent (if you have one)

MEWBURN ELLIS

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

YORK HOUSE
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Description 38

Claim(s) 6

Abstract

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11. I/We request the grant of a patent on the basis of this application.

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SAMPLING KITS, DEVICES AND USES THEREOF

The present invention relates to sampling kits and sampling devices. In particular, it relates to swab kits for taking and analysing biological samples.

Biological samples can be used to obtain and analyse DNA. DNA is usually extracted from such samples using known DNA purification techniques. The aim of such techniques is typically to produce a preparation of DNA roughly 40-150 Kb in length, representing the genetic information within a cell.

Modern DNA isolation techniques exploit both the physical and chemical properties of DNA molecules. Cell lysis and protein denaturation is accomplished simultaneously using proteolytic enzymes, chemical denaturants and heat. DNA can be separated and purified by sorting out (Miller et al, 1998, Nucleic Acids Research, Vol. 16, page 1215) or by reversing binding to a matrix. Modern isolation techniques can allow isolation and purification of DNA in a relatively short time, e.g. 20-30 minutes.

In order to carry out DNA testing on biological material from a subject, it is first necessary to obtain a sample of the biological material. For some types of cells, it is easier to extract DNA than other types of cells. Furthermore, some types of cells are more easily sampled from a subject than others. For DNA analysis, buccal (cheek) cells are often sampled from a subject

since they yield DNA relatively easily and they are easy to obtain.

To obtain buccal cells from a subject (e.g. patient or client), a swab is typically used. Typically, the swab is self-administered by the subject. Typical swabs have a handle and a swab head. The swab head is brushed over the inside surface of the subject's cheek to scrape away some buccal cells. Subsequently, the swab is stored in a container for storage before analysis can be carried out. A particular advantage of buccal cell samples is that such samples can be transported safely by mail. Furthermore, they can be stored for lengthy periods of time whilst still yielding high quality DNA after storage.

Known swabs include: swab TS/19-M of Technical Service Consultants Ltd.; IsoSwab™ (Ref: ISO-SWAB) of Schleicher & Schuell Inc.; Catch-All™ Sample Collection Swab of Epicentre, Madison WI 53713 USA; and the foam-tipped applicator of Whatman International Ltd., Maidstone, Kent ME16 0LS, UK.

The main product on the market for buccal cell sampling has been the Omniswab™ of Whatman International Ltd. (catalogue number WB10-0004). This swab has a tubular handle with a serrated swab head mounted at a slit in a first end. A plunger extends through the length of the handle and away from the second end of the handle. A user can depress the plunger to remove the swab head from the handle. Therefore, after sampling, the swab head can be removed from the handle without the

user touching the swab head. This can help to avoid contamination of the sample with other samples or with other external contaminants.

5 A problem with the Whatman Omniswab™ is that the nature of the swab head detachment system requires that only a narrow surface area of the swab head is available to rub against the cheek for capture of buccal cells. Therefore, although the swab provides a mechanism for detachment of the swab head from the handle, the yield of
10 biological material from the swab head is often unsatisfactory. This problem is exacerbated by the fact that the swab head is made from absorbent material. This material typically swells during processes to isolate DNA from the buccal cells and the material also absorbs DNA.
15 This reduces yet further the yield of DNA from the swab head.

A first development of the present invention has several aspects, which are discussed below. In general, the first development uses head detachment means
20 associated with a container into which the head is to be received. This can reduce the risk of contamination and also allows the number of processing steps involved with sampling and/or analysis of the sample to be reduced.

Preferably, in a first aspect, the first development
25 of the present invention provides: a sampling kit having a sampling device with a sampling head and a handle; and a container for receiving the sampling head, wherein the container has engagement means arranged so that the sampling head is detachable from the handle by engaging

the sampling head with the engagement means and moving the handle with respect to the container.

5 In this first aspect, the sampling head may be removed from the handle in a way which reduces the risk of contamination from a user, in particular by simplifying the construction of the handle.

10 In a second aspect of the first development, the present invention preferably provides a use (or a method of operation) of a sampling device having a handle and a detachable sampling head, the use including the step of engaging the sampling head with engagement means of a container and moving the handle with respect to the container to detach the sampling head from the handle.

15 In this way, the detached sampling head can be separated from the handle so that the sampling head can be located in the container without the handle.

20 Preferably, the sampling device is part of the sampling kit of the first aspect. The optional or preferred features which follow may be applied to the first or second aspect or both.

Preferably, the engagement means is formed on an internal surface of the container. In particular, the container may be a tube which is closed at one end and open at the other end to receive the sampling head.

25 The engagement means may be a lip, step or a barb formed on the internal surface of the container. Typically, the engagement means is shaped and/or directed to allow the sampling head to pass into the container in an entry direction but not in an exit direction. Using

this arrangement, the sampling head can be trapped in the container as it is detached from the handle.

5 Additionally or alternatively, the engagement means may comprise a tapering internal cross section of the container. The internal surfaces of the container may be shaped, for example, so that the distance between opposing internal surfaces of the container changes with distance along the container. In the case where the container is tubular, the change in cross section of the
10 container may be gradual along at least a part of the axial length of the container. In particular, the internal cross section of the container may reduce with depth from the open end of the container. Advantageously, the internal cross sectional area of the
15 container may also correspondingly change with depth. With this arrangement, the sampling head may be inserted into the container until it is jammed between opposing internal surfaces of the container. Further insertion of the handle into the container may then detach the
20 sampling head from the handle, following which the handle can be removed from the container.

25 Additionally or alternatively, the container may have a flexible portion, for example one or more flexible walls. In that case, the engagement means may be the internal surfaces of said flexible walls. A user can detach the sampling head from the handle by inserting the sampling head into the container and holding the sampling head with respect to the container by pressing or squeezing the sampling head by pressing or squeezing an

appropriate part of the container, and then moving the handle to detach the sampling head.

5 The container may include a lid. Typically, the lid is locatable to close the open container, preferably in a sealing engagement with the remainder of the container. Application of the lid to the container once the sampling head is located in the container can help to reduce the risk of accidental contamination of the contents of the container.

10 The engagement means may be a surface of the lid. Preferably, this surface is at least one of the surfaces which faces the internal space of the container once the lid is in place to close the container.

15 In the kit, the lid may be separable from the remainder of the container. In particular, it may be locatable on the sampling device, such as on the handle of the sampling device. The lid may be slidably locatable on the handle of the sampling device. In use, the sampling head may then be placed into the container and the handle withdrawn from the container, e.g. through
20 the lid (the lid may have a corresponding aperture for the handle). The sampling device may be arranged so that the sampling head cannot be withdrawn along with the handle. In such cases, the sampling head may abut
25 against a surface of the lid so that further withdrawal movement of the handle with respect to the lid acts to detach the sampling head from the handle.

Preferably, the surface of the lid which is engageable with the sampling head has a tapering shape.

In particular, when the lid is in place closing the container, the cross section of the lid may increase in the exit (handle withdrawal) direction of the container. This can help the removal of the sampling head from the handle by a wedging action. Preferably, the surface of the lid is conical or frusto-conical.

The sampling head may be attached to an end portion of the handle. For example, the handle may be a shaft and the sampling head may be attached to an end portion of the shaft. In particular, the sampling head may be located around and attached to the end portion of the shaft.

The sampling head may be attached to the end portion of the shaft via one or more releasable attachments.

Such attachments may be re-attachable. However, since the sampling kit is typically manufactured for single use applications (e.g. supplied sterile or clinically clean for biological material sampling), the sampling is typically attached to the end portion of the shaft by one or more breakable attachments. In particular, the head may be attached to the handle via a series of breakable links extending from the end portion of the shaft to the sampling head.

Preferably, the sampling head is hollow. This will usually be the case when the sampling head is located around the end portion of the shaft. There is preferably a space between the end portion of the shaft and the internal surface of the sampling head. Typically, the breakable links connecting the handle to the sampling

head extend across this space to the internal surface of the sampling head. A particular advantage associated with a hollow sampling head is that some biological material to be sampled can be held within the head. This can help to improve the sampling efficiency of the sampling kit.

A further advantage associated with a hollow sampling head is that a retention volume, in which biological material can be retained during an isolation procedure subsequent to a sampling step, is reduced in comparison to a known-hollow sampling head of similar outer dimensions. This is particularly the case if the sampling head is capable of being split to allow access to biological material held within the sampling head.

This advantage can be enhanced by using a material for the sampling head which does not absorb water and/or DNA material. The yield of DNA material from the sampling head can consequently be increased.

Preferably, the sampling head has an undulating outer surface. This can improve the material collecting efficiency of the sampling head, particularly when the material to be collected is in part abraded from its source. Typical surface configurations include ribbed, toothed, bobbled, dimpled, etc. For some applications, a smooth outer surface of the sampling head is suitable. A smooth outer surface may be useful for sampling from people with sensitive mouths or for sampling from open wounds. Furthermore, a smooth outer surface may be useful for cleaning validation of process equipment used

for the manufacture of drugs or chemicals or biological or fluid products. The material of the sample head may be selected to provide a gentle surface texture.

Preferably, the sampling head is formed of a material which does not absorb DNA or water. This allows the yield of DNA to be improved by substantially avoiding absorption of DNA by the sampling head. Similarly, if the sampling head material does not absorb water, aqueous solutions or buffers can be more easily recovered from processes subsequent to the sampling step. Consequently, the sampling head can be left in the container during the subsequent processing steps. This avoids yet another step by which the contents of the container could become contaminated. The material of the sampling head may be a semi-rigid plastics material, such as suitably processed polypropylene, e.g. melt-blown (typically 100% melt-blown) polypropylene. Other materials suitable for the sampling head include polyethylene, PBT (polybutylene terephthalate), nylon 6, nylon 11, polycarbonate, poly(4-methylpentene-1), polystyrene and polyethylene terephthalate. Typically, such material will be formed by melt blowing. In this sense, any polymer suitable for melt blowing can be used to form the sampling head. The fibres of the sampling head typically have a round cross-section. However, square, rectangular, triangular, pie segment and cross-shaped fibres may be used. Such angular fibres can affect the surface texture of the sampling head. For this reason, such materials may allow

a further increase in the yield of biological material from the sampling head.

The container is typically of a standard size and shape. In particular, the container is preferably the same container as used for further processing of the sample collected by the sampling kit. Such further processing may include an assay such as an analysis of the sample collected by chemical, biological, biochemical, forensic, etc. testing or testing involving the clean validation of process equipment used for the manufacture of drugs or chemicals or biological or food products. It is often advantageous to carry out such testing using automated equipment for the introduction of reagents and the subsequent analysis of the product(s). Such automated equipment has the advantage of reliability, reproducibility and standardisation, sample identification tracking, along with a smaller risk of contamination, over conventional non-automated analysis. Furthermore, automated equipment can run very many similar tests at the same time, reducing the overall time required for carrying out a large number of tests. However, such automated equipment is also expensive, and so is usually designed according to a standard. In the field of assays such as high throughput screening and/or DNA assays, the standard has become the use of multi-well plates, i.e. an array of individual reaction containers set out in a predetermined shape, order and geometry with particular dimensions. In particular, the use of 96-well plates or microplates has become commonplace, with each

plate having an 8x12 rectangular array of reaction containers. The plate may either be moulded in one piece, including the containers, or the containers may be separable from a holder having an array of corresponding housings. Higher density well plates are also known for similar applications, e.g. 384 (16 x 24 array) and 1536 (32 x 48 array).

The sampling kit may be used for applications other than DNA assays. In particular, the sampling kit may be used for protein assays and/or for cleaning validation of process equipment to be used in the manufacture of drug products/substances or other pharmaceuticals, foods processing/products, chemicals or biological processing/products.

Preferably, therefore, the container used in the sampling kit is compatible for use in standardised automated assay equipment. In particular, the container is shaped and dimensioned to be suitable for multi-well (e.g. 96-well) testing. The container may be an individual container, or it may be attached to other (typically similar) container in an array suitable for a multi-well (e.g. 96-well) assay.

Typically, the container has an internal depth of at least 10 mm. Preferably the depth is at least 30 mm. Typically the container has an internal depth of at most 200 mm, preferably at most 80 mm.

Typically, the container has an internal width at its open end of at least 4 mm, preferably at least 6 mm.

Typically, the container has an internal width at its open end of at most 15 mm, preferably at most 11 mm.

Overall, the container typically has a volume of about 1.2 ml, but volumes of 0.5, 0.8 and 2 ml (and
5 others in this range) may also be used.

The containers preferably have a rounded internal cross-sectional shape. However, it is possible for the containers to have an angular, e.g. rectangular cross-sectional shape.

10 The sampling device may also be adapted to be more suited to automated assay techniques. The sampling head may be formed so that, once detached from the handle, it presents an aperture. The aperture may be formed at that part of the sampling head through which the handle extends
15 before the sampling head is detached from the handle. Therefore, the aperture may take the shape of the handle at that part of the sampling device. As mentioned above, the sampling head is preferably hollow, so that it may hold sampled material. The aperture typically allows
20 access to the sampled material held within the sampling head. The aperture is therefore preferably of a suitable size and shape to allow access to the interior of the sampling head to, e.g., reagents and/or probes.

25 The aperture may be of a different size and shape to the size and shape of the handle. In particular, the aperture may become enlarged compared to the cross-sectional area of the handle during the detachment process. Dilatation of the aperture may be achieved by respective sides of the sampling head splitting apart.

In the intact sampling device, the sampling head may be formed in different, e.g. longitudinal, segments which are connected along lines of weakness. Subsequent detachment of the sampling head from the handle may cause the segments to break apart, for example around the aperture, thereby dilating the aperture. In some cases, the sampling head may split into two or more parts, thereby exposing sampled material for analysis. In preferred embodiments, the parts of the sampling head which split apart about the inner surface of the container. This can leave the central, e.g. axial, portion of the container free of sampling head, which may allow a probe (e.g. an automated probe) more easily to enter the container. Furthermore, this feature may reduce the risk of a probe accidentally withdrawing the sampling head from the container, which otherwise could lead to cross-contamination of other containers.

The sampling head may be non-symmetrical. In particular, it may have a first width measured in one direction which is greater than a second width measured in another direction. Put another way, the sampling head may have a flattened configuration. This is particularly applicable where the engagement means of the container for detaching the sampling head is the tapering walls of the container. In that case, the sampling head may be detached from the handle by pressing the sampling device, head first, into the container. At the part of the container at which the first width is the same as the internal width of the container, the sampling head

touches opposing internal surfaces of the container.

Further insertion of the sampling head into the container may cause the sampling head to deform, thereby breaking a connection between the sampling head and the handle. The

5 deformation may cause the sampling head to split or partially split into segments. Once the sampling head and handle are no longer connected, further insertion of the handle into the container may assist in splitting the sampling head apart. Removal of the handle back through
10 the sampling head may further separate the segments of the sampling head. The configuration of the remains of the breakable connections between the handle and the sampling head may assist in this.

In the case where the engaging means of the
15 container is a discontinuity such as a step, lip or barb on the internal surface of the container, the change in internal diameter (or internal width) of the container at the discontinuity should usually be at least about 2 mm. Alternatively, the internal width at the narrowest part
20 of the container around the discontinuity should be at least about 2 mm smaller than the width (e.g. the largest width) of the sampling head. In this case, the detachment of the sampling head from the handle typically comes when the sampling device is being removed from the
25 container, catching the sampling head on the discontinuity. Further removal of the handle typically breaks the connection between the sampling head and the handle. The shape of the handle and/or the shape of the broken connection between the handle and the sampling

head may be chosen to allow the sampling head to be split apart (either partially or wholly) as the handle is further extracted from the container.

5 In the case where the engaging means of the container is a surface of the lid of the container, asymmetry of the sampling head is less important, in a similar way to the case where the engaging means is a discontinuity on the internal surface of the container. In this case, the sampling head is typically detached
10 from the handle by being forced against the corresponding surface of the lid. Again, the sampling head may be split apart by interaction between the broken connecting elements attached to the handle. The shape of the surface of the lid also has a role to play. In
15 particular, the lid may have a tapering shape extending into the container (e.g. a wedge shape or a frusto-conical shape). Then the sampling head may be split apart (either wholly or partially) by being forced along the tapering shape of the lid as the handle is withdrawn
20 from the container.

It is mentioned here that the term "lid" is intended to include a cap, stopper or bung or other equivalent closure.

25 Preferably, the sampling head is formed of a material which is sufficiently rigid to allow the sampling head to split open during (or after) detachment of the sampling head from the handle by the engagement means. The rigidity of the sampling head is determined by its shape and by the material used. The rigidity also

determines (in part) the abrasiveness of the sample head, to obtain high yields of cells/DNA. Typically, the sampling head material is selected so that the sampling head is substantially not capable of absorbing water or DNA.

The sampling head is preferably formed in two segments. These segments are typically of similar size and shape. They are typically formed as one piece, with lines of weakness joining them, or they are formed as separate pieces which are subsequently bonded together (the bonds forming the lines of weakness). During detachment from the handle, the segments preferably split apart.

The sampling head is preferably joined to the handle by a series of breakable attachment elements. These may be attachment fingers or lattices. Preferably, these elements break at their connection with the sampling head. In this way, once the sampling head is detached from the handle, the connection elements remain attached to the handle and are removable from the container with the handle. In order to assist with breaking open the sampling head on removal of the handle, the connection elements are typically protruding elements. They may, for example, protrude from the handle to a width as great as the width of the sampling head, or slightly smaller. They may provide the sampling head with rigidity, particularly where the sampling head has a flattened configuration. They may be attached to the sampling head

at a line of weakness, e.g. at a join between segments of the sampling head.

Usually, the dimensions of the sampling head are chosen with respect to the container which will be used with the sampling device. For multi-well applications in particular, the length of the sampling head may be about 10-20 mm, preferably about 17 mm. The width in one direction may be about 5-8 mm, preferably about 7 mm. The width in another direction may be about 2-5 mm, preferably about 3-3.5 mm.

The engagement means may be formed by an extension or attachment of the lid. In particular, when the lid is in place closing the container, the engagement means, although connected to the lid, may be located some distance away from the opening end of the container. The lid may have an extended neck portion which extends into the container, towards the closed end of the container. Preferably, when the lid is in place closing the container, the neck portion extends at least 50%, or preferably at least 75% along the longitudinal axis of the container, towards the closed end (e.g. the base) of the container. Having the engagement means relatively close to the base of the container allows the sampling head to be detached from the handle at a location relatively close to the base of the container. In this way, the sampling head is less likely to become stuck between the walls of the container at a location away from the base of the container.

The extended neck may include guide means. This guide means may cooperate with corresponding means (e.g. a groove, ridge or lug) formed on the handle. The guide means preferably extends along a predetermined portion of the neck, from the engagement means. In operation, an end of the guide means away from the engagement means may provide a stop limit for movement of the handle with respect to the next. Preferably, this stop limit allows the swab head to be detached from the handle by the engagement means before the stop limit is reached. After detachment of the sampling head from the handle, the handle and lid may be removed from the container together, e.g. by pulling the handle. The cooperation of the stop limit of the guide means and the handle can thereby allow removal of the lid and handle in a single operation. This may, for example, be done robotically, e.g. prior to DNA isolation processing.

An important factor in assessing the risk of contamination of a sample is the number of steps taken during the lifetime of the sample. The steps include the taking and storage of the sample, but also include subsequent processing steps and/or assay of the sample.

Handling of a fluid sample can be simplified by allowing the sample to be absorbed into an absorbent material such as filter paper. Subsequent drying of the paper can allow retention of useful biological material in or on the paper. Typically, this can be handled more easily than the original fluid sample, e.g. parts of the

paper can be cut away for further analysis by rehydration of the sample.

5 However, the transfer of sample to the filter paper is inefficient, since it is difficult to ensure that a usefully large proportion of the sample held by, e.g., a swab is transferred to the filter paper by wiping the swab on the paper.

10 This problem is addressed by another, independent development (second development) of the present invention. In a first aspect, this development provides a sampling kit having a sampling device with a sampling head, and absorbent cover means which is configurable to receive the sampling head to allow, in use, sample held by the sampling head to transfer to the cover means.

15 In a second aspect of this second development, the present invention provides a use of a sampling kit, including the step of transferring sample from a sampling head of a sampling device to an absorbent material by receiving the sampling head in a cover means formed of
20 the absorbent material.

The absorbent cover means may be a sheet of absorbent material configured to define a shape which is able to cooperate with the shape of the sampling head. In particular, the cover means may be shaped to enclose
25 or embrace (at least partially but preferably wholly) the sampling head. The cover means may be a sleeve, collar or tube and may be open or closed.

Absorbent material is known which can not only help in the storage of biological samples, but which also can

initiate processing of the sample. An example of such material is IsoCode™ paper, available from Schleicher & Schuell (P.O. Box 4, D-37582 Dassel, Germany). Preferred embodiments of the present invention incorporate similar material. Accordingly, the cover means is preferably formed from a material which is capable of interacting with biological material to release nucleic acid(s).

The biological material may be cellular material or virus particles, for example.

The interaction between the biological material and suitable material for the cover means may be a disrupting or lysing interaction for cellular material or a disrupting interaction for virus particles. Typically, the kit is to be used for assays of double stranded DNA (dsDNA), as found in nucleated cells, but is also suitable for other DNA such as ssDNA or other nucleic acids such as RNA (e.g. ssRNA, dsRNA, tRNA or rRNA), mitochondrial DNA, plasmid/bacterial DNA samples, etc.

In general, the absorbent material is preferably an impregnated (or otherwise treated) paper or fabric which is capable of yielding amplifiable nucleic acid from suitable biological material, such as buccal cells.

Typically, the kit further includes a container for holding the sampling head. In that case, the absorbent covering means is preferably configurable to be interposed between the sampling head and an inner surface of the container. Preferably, in use, the covering means is pressed between the sampling head and the inner surface of the container.

In the kit, before use, the cover means may be disposed in the container, i.e. prior to the sample head being received by the cover means. In that case, the cover means may be a lining (e.g. a partial lining) of the container. An advantage of having the cover means pre-placed in the container of the kit is that the user does not need to perform this step. This eliminates a step from the sampling process and so reduces the risk of contamination.

Alternatively, before use, the container and the cover means may be separate. In that case, the use may include the step of locating the cover means in the container. This step may take place before or after the sampling head is received by the cover means.

Preferably, the kit or use is according to the first development of the invention, with absorbent cover means provided which is configurable to be interposed between the sampling head and an internal surface of the container. Typically, this allows an efficient transfer of sample held by the sampling head to the cover means.

The second development of the invention may be combined with any preferred feature according to the first development and vice versa.

Preferred embodiments of the invention will now be described, by way of example only, with reference to the accompanying drawings, in which:

Fig. 1 is a schematic longitudinal cross sectional view of a kit according to an embodiment of the invention.

Fig. 2 is a schematic lateral cross sectional view along line A-A' in Fig. 1.

Fig. 3 is a schematic longitudinal cross sectional view of the kit of Fig. 1 with the swab further inserted.

5 Fig. 4 is a schematic lateral cross sectional view along line B-B' in Fig. 3.

Fig. 5 is a schematic longitudinal cross sectional view of the kit of Fig. 3 with the swab still further inserted.

10 Fig. 6 is a schematic lateral cross sectional view along line C-C' in Fig. 5.

Fig. 7 is a schematic longitudinal cross sectional view of the kit of Fig. 5 with the handle of the swab being removed from the container.

15 Fig. 8 is a schematic lateral cross sectional view along line D-D' in Fig. 7.

Fig. 9 is a schematic longitudinal cross sectional view of a container for use in a kit according to an embodiment of the present invention.

20 Fig. 10 is a schematic longitudinal cross sectional view of an alternative container for use in a kit according to an embodiment of the present invention.

Fig. 11 is a schematic longitudinal cross sectional view of a kit according to an embodiment of the
25 invention.

Fig. 12 is a schematic longitudinal cross sectional view of a kit according to another embodiment of the invention.

Fig. 13 is a schematic longitudinal cross sectional view of an alternative stopper for use with the kit shown in Fig. 12.

5 Fig. 14 is a schematic lateral cross sectional view along line E-E' in Fig. 13.

Fig. 15 is a schematic longitudinal cross sectional view of another alternative stopper for use with the kit shown in Fig. 12.

10 Fig. 16 is a schematic lateral cross sectional view along line F-F' in Fig. 15.

Fig. 17 is an enlarged, schematic, exploded view of one end of a swab for use in or with embodiments of the invention.

15 Fig. 18 is an enlarged, schematic, exploded view of one end of another swab for use in or with embodiments of the invention.

Fig. 19 is an enlarged, schematic, exploded view of one end of a further swab for use in or with embodiments of the invention.

20 Fig. 20 is an enlarged, schematic, exploded view of one end of a further swab for use in or with embodiments of the invention.

25 Fig. 21 is a schematic, exploded, partial longitudinal cross section of a kit according to an embodiment of the invention.

Fig. 22 is a schematic longitudinal cross section of part of a kit according to another embodiment of the invention.

Fig. 23 is a schematic longitudinal cross-section of a kit according to another embodiment of the invention.

Fig. 24 shows the kit of Fig. 23 with the stopper in place closing the container.

5 Fig. 25 shows the kit of Figs. 23 and 24 after detachment of the sampling head from the swab handle.

Fig. 26 is a schematic longitudinal cross-section of a kit according to an alternative embodiment of the invention.

10 Fig. 27 shows the kit of Fig. 26 with the stopper in place closing the container.

Fig. 28 shows the kit of Figs. 26 and 27 during removal of the stopper and swab handle from the container.

15 Fig. 29 shows a schematic view of the stopper only, along line G-G' in Fig. 27.

Figs. 1 to 8 illustrate a mode of operation of a kit according to an embodiment of the invention. Like features are given the same reference numerals in these drawings.

20 Fig. 1 shows one end of a swab 10, including a shaft 12 at one end of which is formed a swab head 14. Such a swab is illustrated in more detail in Fig. 17. In Fig. 17, there is shown an enlarged exploded view of the structure of the swab 10. The shaft 12 narrows to a constriction 16 which leads to a flattened tongue portion 18. Connection elements 20 project from the narrow sides of tongue portion 18. The swab head 14 is composed of two opposing segments 14a and 14b. Segments 14a and 14b

25

are lightly bonded to each other at their peripheries, embracing the tongue 18. Connection elements 20 provide some extra stiffness to the structure and may be sandwiched in the bond between the segments 14a and 14b.

5 The upper ends 22a and 22b of the segments 14a and 14b form a collar around the constriction 18 and may be lightly bonded to the surface of the constriction 18. There is a hollow space between the inside surfaces of the segments 22a, 22b and the tongue 18.

10 Swab head 14 is made from melt blown polypropylene, typically 100% melt blown polypropylene. The surface of the swab head 14 is ridged. This allows the swab to rub or scrape more sample from a sampling location. Typically, the swab is used to sample buccal (cheek) cells from the inside of a subject's mouth. However, the
15 swab may also be used to take forensic samples, for example. Polypropylene has the advantage that it does not absorb water or DNA. For this reason, it is efficient at transferring high yields of sample. A
20 suitable swab is the Texwipe scourswab, model no. TX8641, produced by the Texwipe Company LLC, Upper Saddle River, New Jersey 07458, USA. Such a swab has typical dimensions as follows: swab head 16.8 mm long and 7 mm wide at widest point; swab shaft (including tongue 18)
25 146 mm long and 3 mm wide.

In a typical use, the first step is the sampling step, e.g. a subject rubs the inside surface of their cheek to load cellular material onto the swab head. The cellular material is loaded on the outer surface of the

swab head (e.g. between ridges on the swab head) and in the space between the segments 22a,b and the tongue 18. Subsequent steps are shown by Figs. 1-8, which are described in detail below.

5 In Fig. 1, the swab 10 is inserted, head 14 first, into the open end of a tubular container 30. Container 30 has a generally circular cross section (as shown by Fig. 2) but is not wholly cylindrical. Instead, the base 32 of the container 30 is rounded. This allows the
10 analysis of small volumes of fluid in the container 30. Also, the side walls 34,36 of the container 30 taper towards each other in a direction away from the open end of the container 30. For convenience, opposing side walls 34,36 are labelled separately but of course in the
15 present case of a container 30 with a cylindrical cross section, there is a single, continuous side wall.

 Fig. 2 shows a lateral cross sectional view along line A-A' in Fig. 1. The swab head 14 has a generally oval (or pointed oval) cross sectional shape, and the
20 tongue 18 has a generally rectangular cross sectional shape. With the swab head 14 in the position shown in Figs. 1 and 2, the swab head 14 does not touch both of the inner surface of the side walls 34,36.

 The swab head 14 is pushed further into the
25 container 30 in Fig. 3. At the point shown in Fig. 3, the swab head is pressed lightly between the side walls 34,36 due to the tapering of the side walls 34,36. Fig. 4 shows a lateral cross section along line B-B' in Fig. 3. Fig. 4 shows that the cross sectional shape of the swab

head 14 changes due to the deformation imposed by the side walls 34,36. The deformation involved is the forcing-apart of the segments 14a,b which make up the swab head 14.

5 Fig. 5 shows the subsequent step where the swab head 14 has been forced as far as it can go into the container 30. At this point, the swab head is jammed between the side walls 34,36 of the container 30. Further forcing of the swab into the container (by a user pressing down on shaft 12) moves the shaft 12 with respect to the swab head 14. The tongue 18 pierces the base of the swab head 14, until the tongue abuts against the inner surface of the base of the container 30. Thus, the shaft 12 moves with respect to the swab head 14 and the constricted portion 16 of the shaft 12 is forced into the swab head 14. The wider portion of the shaft 12 is thereby interposed between the upper portions 22a and 22b of the swab head, forcing the segments 14a,b apart slightly at this location. Fig. 6 shows that the segments 14a,b are moved apart further than in Fig. 4.

20 Finally, in Fig. 7, the shaft 12 is pulled up from the container 30. The swab head 14 at least partially breaks into its component segments 14a,b by the withdrawal of the tongue 18 and particularly by the broken projecting connection elements 20 which help to break the light bond between the segments 14a and 14b. As shown by Fig. 8, the segments 14a and 14b break away from each other once the shaft 12 is removed from the container. This leaves a space 38 in the container along

the axis of the container. Sample held within the swab head is therefore easily accessible, thereby improving the efficiency of the sampling process. Furthermore, the space 38 left along the axis of the container means that it is not necessary to remove the remains of the swab head from the container, since the sample is easily accessible along the axis of the container. The need for removal of the swab head would introduce an element of risk of contamination of the sample. Elimination of this need eliminates that particular risk of contamination.

A particular advantage associated with this embodiment is that the space 38 left in the container allows the easy application of automated assaying equipment to the kit. The space 38 allows sample to be extracted easily from the container using automated probes, and equally allows the easy introduction of buffers and/or reagents into the container using automated probes.

Suitable containers 30 for the kit are containers which also can be arranged in an array to allow multiple testing of samples held in each container. In particular, the containers can be containers (either fixed or removable) for 96 well plates (or microtubes), a standard 8x12 format for genomic automated processes such as DNA testing, e.g. > 1ml tubes. Suitable products include the Riplate™ microtube rack systems (catalogue numbers 602100, 602200, 602300, 602350, 602101, 602201, 602110, 602112, 602400, 602500, 602450, 602550) and the 2.4ml and 1ml deep well plates of the same supplier

(catalogue numbers DW850301, DW850276), all available from Elkey Laboratory Products (UK) Ltd., Basingstoke, Hampshire RG24 8NA, UK. Other suitable products are the 2.2ml storage plate, the 2.2ml storage plate Mark II and the 1.2ml storage plate (catalogue numbers AB-0932, AB-0661, AB-0564, respectively), all available from Abgene, Epsom, Surrey KT19 9AP, UK. Similar plates are available from other manufacturers.

Following sampling and introduction and separation of the swab head into the container, DNA testing may be carried out. Suitable DNA isolation kits for use with embodiments of the present invention include those using magnetic bead and filter techniques, e.g. QIAamp DNA blood mini kit (catalogue no. 51104) and QIAamp 96 DNA blood kit (catalogue no. 51161), both available from Qiagen Ltd., Boundary Court, Gatwick Road, Crawley, West Sussex RH10 2AX, UK. Also suitable are nucleospin multi-96 blood kit (catalogue no. K-3062-1) and nucleospin blood kit mini kits (catalogue no. K-3052-1), both available from BD Biosciences Clontech UK, 21, In Between Towns Road, Cowley, Oxford OX4 3LY, UK. Also suitable is Agowa Mag Maxi DNA isolation kit, from AGOWA GmbH Glienicke Weg 185, D-12489, Berlin, Germany. Also suitable are magnetic bead kits under development at DRI (DNA Research Innovation Ltd), 940 Cornforth Drive, Sittingbourne Research Centre, Kent ME9 8PX.

Alternative types of container are illustrated in Figs. 9 and 10. In Fig. 9, the container 40 has a rounded base 42 with a generally cylindrical outer

surface 44. In other words, the container does not have tapering walls. Instead, the inner surface of the side walls of the container presents a step 48 which increases the cross section or cross sectional area of the container in a stepwise fashion in a direction away from the open end 46 of the container. Substituting now the container 40 of Fig. 9 into the sequence of events shown in Figs. 1-8, the cross section of the open end 46 of the container is just large enough to allow the intact swab head to be inserted into the end 46, but with some deformation of the swab head 14 due to pressure against side walls 50,52. The cross section of the container may taper at the open end 46 to facilitate insertion of the swab head into the container.

When the swab head passes the step 48, the pressure on the sides of the swab is relaxed and the swab head (being slightly elastic) can return to its original shape. Subsequently, upwards movement of the swab forces the swab head 14 against step 48. The abrupt reduction in cross section of the container in the upwards direction does not assist the swab head in passing through the constriction. Consequently, the swab head is trapped against the step 48. If the swab handle (shaft 12) is pulled up further, the swab head detaches from the handle and falls back into the container 40. Thus, the risk of contamination of the sample is avoided during the detachment of the swab head from the shaft 12.

Fig. 10 shows a similar container 54 to the container 40 shown in Fig. 9. In Fig. 10, the container

54 has a tapering section 56 at its inside side surface. This taper is sufficient to deform the swab head 14, but insufficient to detach it from the shaft 12. The tapering section ends abruptly in a step 58 which widens the cross section of the container again. Removal of the shaft 12 from the container causes the swab head to become detached due to abutment with step 58, in a similar way to that described with respect to Fig. 9.

Fig. 11 shows another embodiment of a kit 60 according to the present invention. The kit as illustrated is (schematically) as it would appear to a user before using the kit. A swab 10 is located in a container 62. Again, the swab has shaft 12 and swab head 14. The container has a lid 64 which fits over the side walls of the container. Lid 64 has a hole at its centre through which the shaft 12 of the swab extends. For use, the swab is removed from the container 62 by removing the swab 10 and the lid 64 together from the rest of the container. The lid 64 therefore remains in place with respect to the shaft 12. The swab is used to collect a sample (with the lid still on the shaft) and then the swab is placed back inside the container 62 and the lid reattached over the side walls of the container.

Subsequently, the user draws the shaft of the swab upwardly with the lid remaining in place with respect to the rest of the container. When the swab head 14 reaches the lid 64, it presses against it due to the upwards force exerted on the shaft 12 by the user. The inner surface 66 of the lid detaches the swab head from the

shaft 12 and the shaft can be removed completely from the container. The detached swab head then falls to the base of the container for further processing/analysis, for example as referred to above with respect to DNA assays or pharmacogenomic or forensic applications.

Figs. 12-16 illustrate variations on the embodiment described with respect to Fig. 11. In Fig. 12, the lid is a stopper 70. The abutment surface 72 of the stopper facing the inside of the container is shaped to facilitate removal of the swab head. In particular, the abutment surface 72 of the stopper tapers towards the swab head 14. As the swab is pulled out from the container, the swab head 14 is wedged open into its components segments 14a,b by the tapering abutment surface 72. The surface 72 in Fig. 12 is shown as part of a cone, but other shapes can be used. In particular, the shape can be a partial curved cone which tapers non-uniformly, e.g. as shown by surface 74 arranged around hole 76 in Figs. 13 and 14. Additionally or alternatively, the surface may include a blade section 78, as shown by Figs. 15 and 16. This assists in separating the segments of the swab head.

The advantage of the separation of the swab head has already been described with respect to Figs. 1-8 and will not be repeated here.

Figs. 23-25 show an alternative embodiment to the embodiments shown in Figs. 12-16. In Fig. 23, a container 100 receives an assembly of a swab (consisting of handle 12 and swab head 14) and a stopper 102.

Stopper 102 has a sealing cap 104 and an extended neck portion 106. A cylindrical bore 108 is formed along the longitudinal axis of the neck portion 106 and cap 104. Within the cylindrical bore 108 is located the shaft 12 of the swab. The fit between the shaft 12 and the bore 108 is such that stopper 102 and handle 12 are slidable with respect to each other.

Fig. 24 shows the kit of Fig. 23 when the stopper is located within container 100. Cap 104 forms a seal (e.g. a fictional seal) with the open end of container 100. As shown in Fig. 24, when the stopper 102 is in place closing the container 100, the neck portion 106 extends between two-thirds and three-quarters of the axial length of the container 100. Beyond the lower end 110 of the neck 106 is located the swab head 14. Due to the length of the neck 106, the swab head 14 is located close to the closed end (i.e. base) of container 100.

Fig. 25 shows the kit of Figs. 23 and 24 after the swab head 14 has been detached from the swab handle 12. The mode of detachment of the swab head 14 from handle 12 is similar to that described in respect of Figs. 12-16. However, a significant difference between this embodiment and the embodiments described in relation to Figs. 12-16 is the positioning of the tapering contact surface 112 with respect to the container 100. Since it is the abutment between the swab head 14 and surface 112 which acts to detach the swab head 14 from the handle 12 (on relative movement between the swab handle 12 and the stopper 102), the detachment takes place at a position

which is deep inside container 100. For this reason, the swab head 14 has only a small distance to travel to rest at the base of container 100. This reduces the likelihood of the swab head becoming wedged sideways, for example, at an upper portion of the container 100. An advantage here is that, by ensuring that the swab head 14 is located deep within container 100, it is less likely that the swab head will interfere with subsequent processing. In particular, ensuring that the swab head 14 does not become trapped at a shallow portion of container 100 allows probes (e.g. robotic probes) to be inserted part way into container 100 during subsequent processing of the biological sample (e.g. DNA assaying).

Figs. 26-29 show a modification of the embodiment described in relation to Figs. 23-25. Stopper 102 again has an extended neck portion 106. However, in this case, a pair of slots 114 is formed in neck portion 106. Slots 114 extend axially from end 110 of the neck portion to a stop limit 116. Slots 114 communicate with cylindrical bore 108. Slots 114 are shown in Fig. 29.

Handle 12 includes protruding lugs or arms 118. These are located close to the swab head 14. Arms 118 are shaped to be able to slide along slots 114 up to the stop limit 116.

Fig. 27 shows the kit after cap 104 has closed the open end of container 100. Furthermore, handle 12 has been moved upwardly with respect to stopper 102 in order to detach swab head 14 from the handle. The upwards

travel of handle 12 is limited by the abutment of arms 118 with stop limit 116 of slots 114.

As shown in Fig. 28, the handle 12 and the stopper 102 can be removed from the container by pulling on handle 12. In this way, the number of steps required to prepare the sample for analysis can be reduced. In particular, the removal of stopper 102 with handle 12 is suited to robotic processing of the sample. The reduction in the number of processing steps and the suitability for large scale robotic analysis can reduce the risk of contamination (including cross-contamination) of the sample.

The structure of the swab head itself has already been described with reference to Fig. 17. Figs. 18-20 illustrate modifications of the swab structure, in particular modifications of the size and shape of the projecting connection elements 20. In Fig. 18, the connection elements 20 are directed to curve upwardly from the tongue 18 with respect to the swab head. This can assist in breaking the swab head segments apart when the tongue 18 moves downwardly with respect to the swab head 14. In Fig. 19, the connection elements 20 are directed to curve upwardly from the tongue 18. This can assist in breaking the swab head segments apart when the tongue 18 moves upwardly with respect to the swab head 14. In Fig. 20, the connection elements 20 are enlarged compared to the connection elements of the embodiment illustrated by Fig. 18. This can provide extra stiffness to the swab head as a whole and also can assist in

breaking the swab head segments apart during movement of the tongue 18 with respect to the swab head.

Another embodiment of the invention is illustrated in Fig. 21. The kit includes a swab 10, a sleeve of paper 80 and a container 82. The sleeve of paper 80 is shaped and sized to fit snugly around the swab head 14. The paper is absorbent, typically absorbing water and/or aqueous solutions. In particular, the snug fit allows sample held by the swab to be transferred (e.g. by leaching) from the swab to the paper sleeve 80. This is enhanced by the fact that polypropylene (the material of the swab) is non-absorbent.

In one embodiment, after the swab head 14 is located within the sleeve 80, the combination is placed into the container 82 for storage. The container may be a container, e.g. similar to one of the containers illustrated and described with respect to Figs. 1-8 or Figs. 9 and 10 or Figs. 11-16.

In another embodiment, the sleeve is first fitted within the container 82 before the swab head is located within the sleeve. An advantage of this is that the sleeve need only be handled by way of the outside surface of the container. This can avoid contamination problems. The sleeve is a snug fit within the container 82. In this way, the sleeve can be pressed between the swab head 14 and the inside surface 84 of the container 82. This can assist in the efficient transfer of sample from the swab head 14 to the sleeve 80.

Fig. 22 illustrates an embodiment of a modified container for use, e.g. with the kit arrangement of Figs. 1-8. In this figure, a container 86 of a similar shape to the container 30 of Fig. 1 is shown. A partial lining 88 of absorbent material is located on the inside surface of the container 86. The lining 88 is located at or close to the final location of a detached (and split) swab head in the container 86 after use of the kit. Use of a tapering container means that the swab head 14 is detached from the shaft 12 due to pressure between the inner surface of the container 86. Since the inner surface of the container is lined with the absorbent lining, the swab head is pressed against this lining. This further improves the transfer of sample from the swab head to the lining.

The absorbent material used in these embodiments is typically an impregnated sample collection paper, e.g. a treated filter paper. The sample is typically collected from the swab head onto the paper and allowed to dry.

This can be an efficient, stable and cost-effective method for storing biological samples. The treated paper can yield high quality nucleic acid for PCR amplification. The treatment of the paper allows the paper to disrupt intact cells and release nucleic acids from nucleated cells in blood, eukaryotic cells, bacteria or virus particles. After drying, the sample can be rehydrated and then amplifiable nucleic acids can be eluted from the paper. Alternatively, DNA (for example) can be amplified from the paper itself. The paper is

treated in such a way that substances which inhibit PCR reactions (e.g. haemoglobin in blood samples) become fixed to the matrix of the paper and are not released with template nucleic acids. Suitable material is available in the form of modified filter paper called IsoCode™ (e.g. catalogue no. 495020, 495000, 495005, 495015, 495017, 495025), available from Schleicher & Schuell, P.O. Box 4, D-37582 Dassel, Germany or Keene, NH 03431, USA. The content of US patent numbers 5939259, 6168922, 5807527 is incorporated herein by reference.

Use of the treated absorbent paper in the container allows the paper to process (i.e. commence nucleic acid release) from the sample transferred to it from the swab head during shipment of the sample. This can greatly reduce the time taken to process the sample and can remove yet another step from the processing of the sample which could otherwise give rise to a risk of contamination.

Use of the swab described provides a high yield of biological material due to the non-absorbent nature of the swab head material, and also due to the large surface area of the swab head and its rigid surface (which makes it relatively abrasive). The absorbent paper can allow longer term storage of the sample at room temperature.

The embodiments described above are examples only. Modifications of these embodiments, further embodiments and modifications thereof will be apparent to the skilled person and as such are within the scope of the invention.

CLAIMS:

1. A sampling kit having:

a sampling device with a sampling head and a handle;

5 and

a container for receiving the sampling head,

wherein the container has engagement means arranged so
that the sampling head is detachable from the handle by
engaging the sampling head with the engagement means and
10 moving the handle with respect to the container.

2. A sampling kit according to claim 1 wherein the
engagement means is formed on an internal surface of the
container.

15

3. A sampling kit according to claim 2 wherein the
engagement means is a step or a barb formed on the
internal surface of the container and shaped and/or
directed to allow the sampling head to pass into the
20 container in an entry direction, but not in an exit
direction, to detach the sampling head from the handle.

4. A sampling kit according to claim 2 wherein the
engagement means comprises a tapering internal cross
25 section of the container.

5. A sampling kit according to claim 1 wherein the
container includes a lid and the engagement means is a
surface of the lid.

6. A sampling kit according to claim 5 wherein the lid is slidably locatable on the handle of the sampling device, to enable detachment of the sampling head by the engagement means.
7. A sampling kit according to claim 5 or claim 6 wherein the engagement means has a tapering shape to assist segmentation of the sampling head.
8. A sampling kit according to any one of claims 1-7 wherein the sampling head is at least partially hollow.
9. A sampling kit according to any one of claims 1-8 wherein the sampling head is formed of a material which does not absorb DNA and/or water.
10. A sampling kit according to any one of claim 1-9 wherein the container suitable for multiple well testing, such as part of a 96, 384 or 1536 well plate or is suitable for use in such a well plate or microplate.
11. A sampling kit according to any one of claims 1-10 wherein the sampling head is formed so that, once detached from the handle, it presents an aperture.
12. A sampling kit according to claim 11 wherein, in use, the aperture becomes enlarged compared to the cross-

sectional area of the handle during detachment of the sampling head from the handle.

5 13. A sampling kit according to claim 12 wherein the sampling head is splittable into two or more parts, thereby exposing sampled material for analysis.

10 14. A sampling kit according to claim 13 wherein the parts of the sampling head which split apart abut the inner surface of the container.

15 15. A use of a sampling kit according to any one of claims 1-14 to take a biological sample from a subject, with the optional further steps of storing and/or processing the sample.

20 16. A use of a sampling device having a handle and a detachable sampling head, the use including the step of engaging the sampling head with engagement means of a container and moving the handle with respect to the container to detach the sampling head from the handle.

25 17. A use according to claim 15 or claim 16 wherein the sampling head is detached from the handle by pressing the sampling device, head first, into the container and, optionally, subsequently removing the handle.

18. A use according to claim 17 wherein pressing of the sampling head into the container causes the sampling head

to deform by engagement with the engagement means, thereby breaking a connection between the sampling head and the handle.

5 19. A use according to claim 18 wherein subsequent movement of the handle with respect to the sampling head causes the sampling head to split or partially split into segments.

10 20. A use according to claim 15 or claim 16 wherein detachment of the sampling head from the handle occurs during withdrawal of the handle from the container, catching the sampling head on the engagement means.

15 21. A sampling kit having a sampling device with a sampling head, and absorbent cover means which is configurable to receive the sampling head to allow, in use, sample held by the sampling head to transfer to the cover means.

20 22. A sampling kit according to claim 21 wherein the absorbent cover means is a sheet of absorbent material configured to enclose or embrace (at least partially but preferably wholly) the sampling head.

25 23. A sampling kit according to claim 21 or claim 22 wherein the cover means is formed from a material which is capable of interacting with biological material to release nucleic acid(s).

24. A sampling kit according to claim 23 wherein the absorbent material is an impregnated paper or fabric which is capable of yielding amplifiable nucleic acid from suitable biological material, such as buccal cells.

25. A sampling kit according to any one of claims 21-24 further including a container for holding the sampling head and wherein the absorbent covering means is configurable to be interposed between the sampling head and an inner surface of the container.

26. A use of a sampling kit, including the step of transferring sample from a sampling head of a sampling device to an absorbent material by receiving the sampling head in a cover means formed of the absorbent material.

27. A use according to claim 26 wherein the sampling kit is according to any one of claims 1-14, 21-25

28. A use according to claim 26 or claim 27 wherein, prior to the sample head being received by the cover means, the cover means is disposed in the container.

29. A use according to claim 26 or claim 27 including the step of locating the cover means in the container, before or after the sampling head is received by the cover means.

30. A use according to any one of claims 26-29 further including the step of carrying out at least one of a DNA/RNA assay, forensics, chemical, biological, microbiological sampling, or cleaning validation of

5 process equipment to be used for pharmaceuticals, foods, proteins or biological species.

Fig. 1

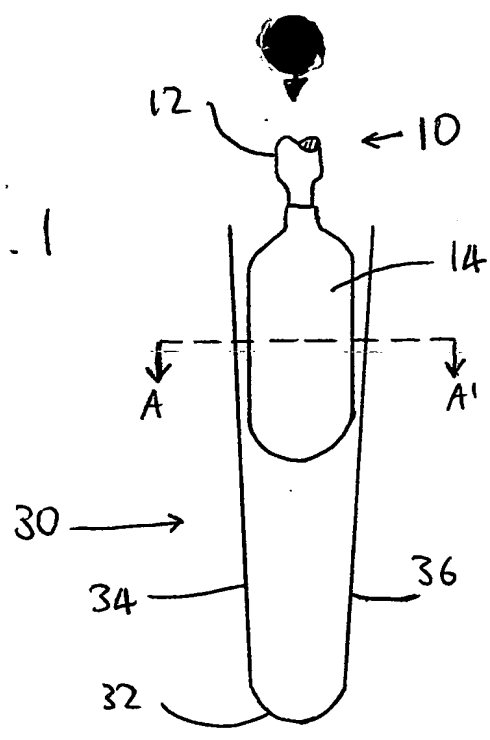


Fig. 3

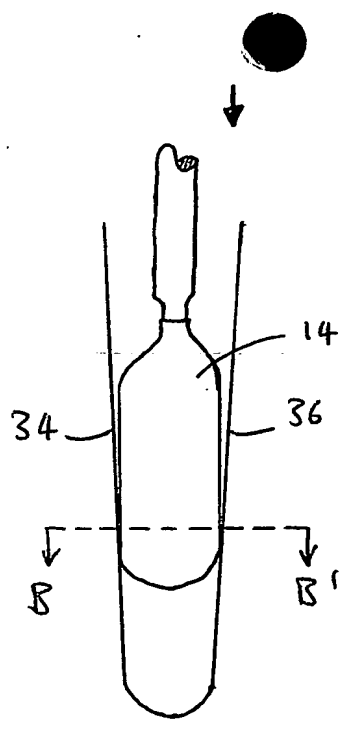


Fig. 2

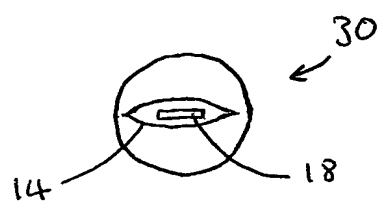


Fig. 4

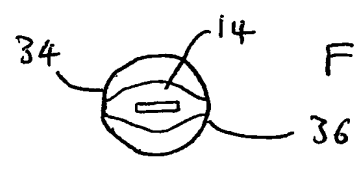


Fig. 5

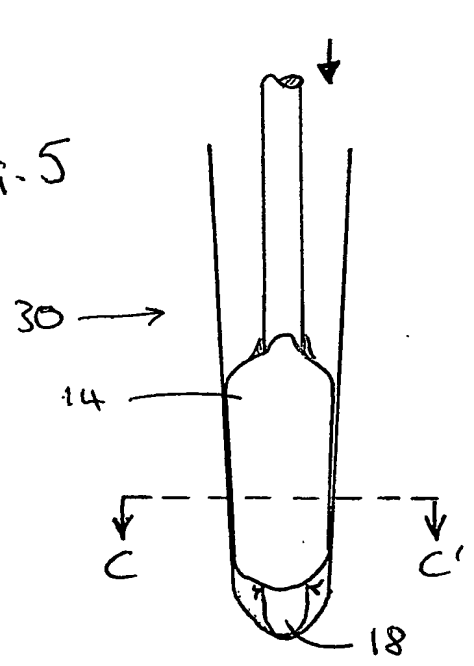


Fig. 7

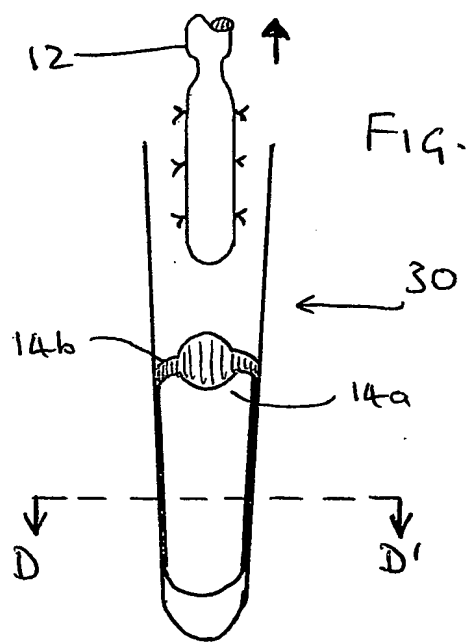


Fig. 6

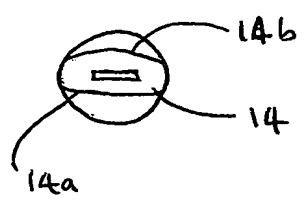
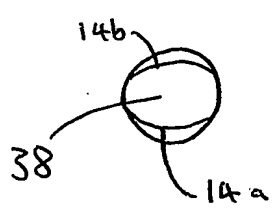
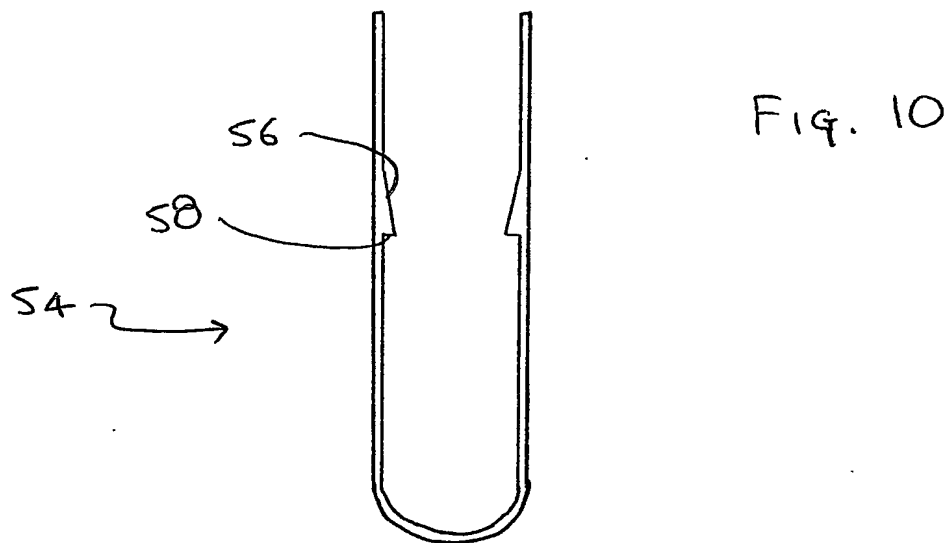
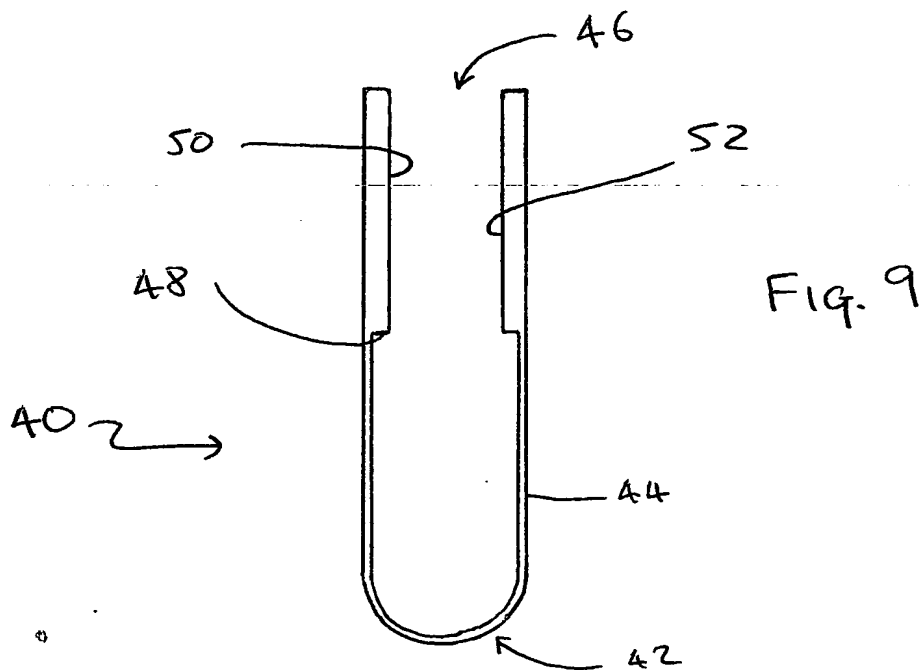
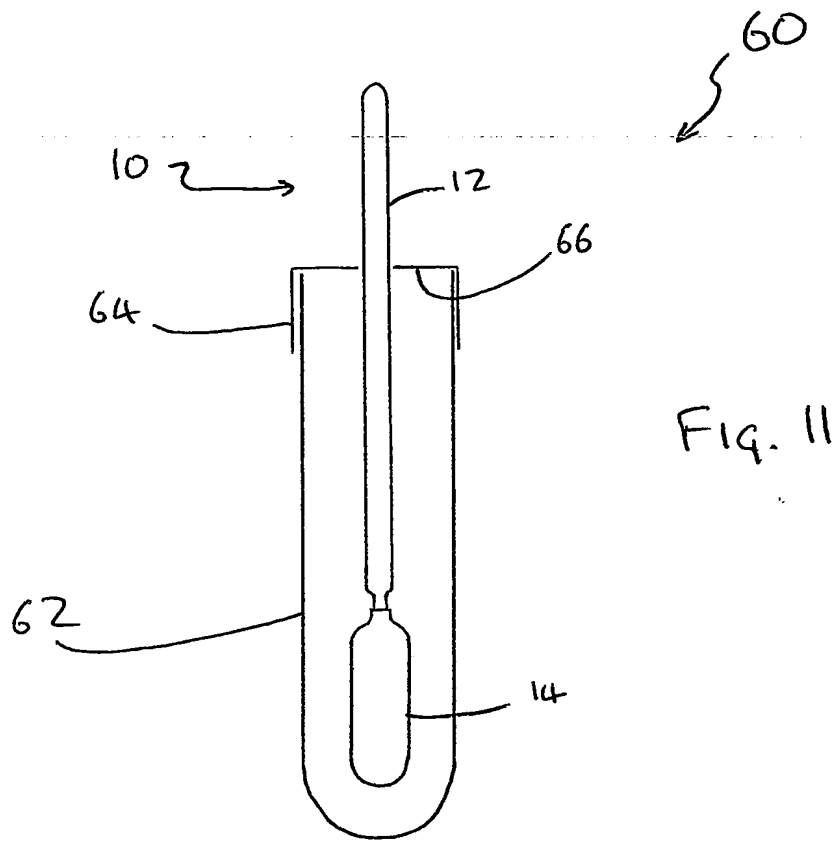


Fig. 8







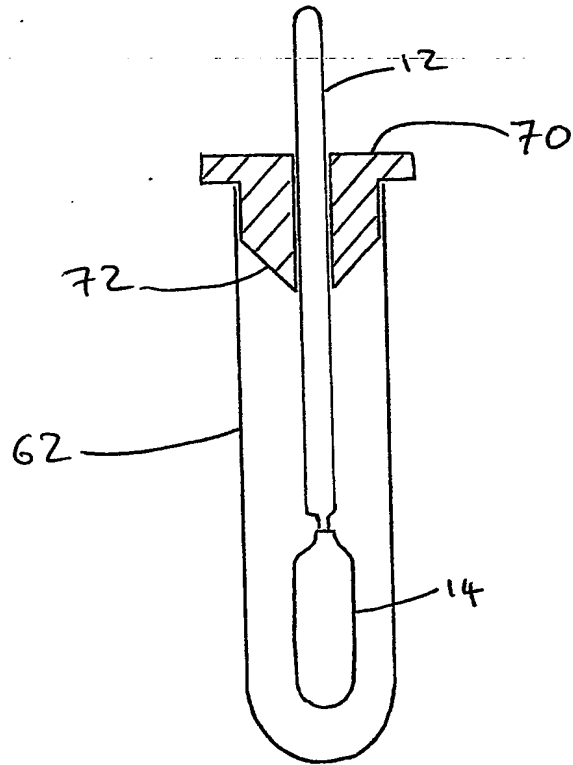


Fig. 12

Fig. 13

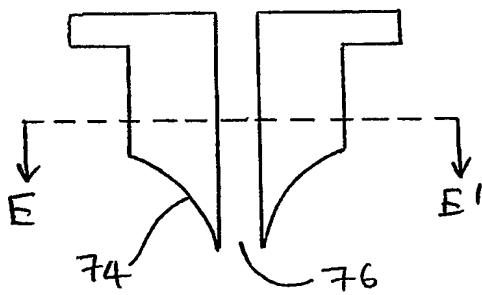


Fig. 15

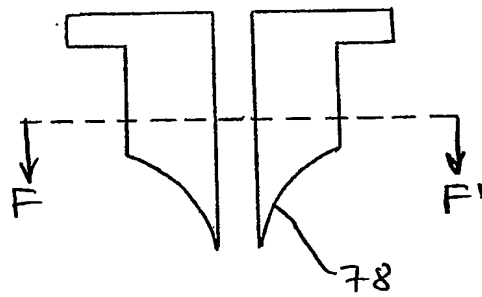


Fig. 14

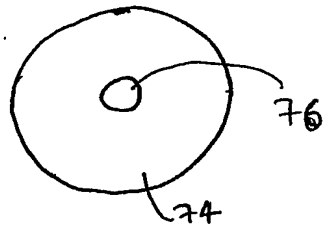
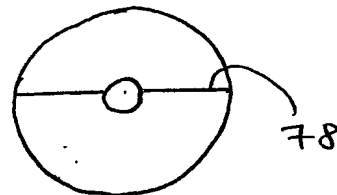
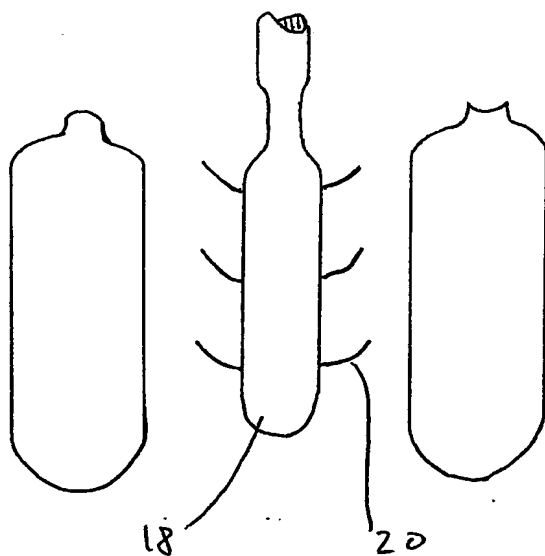
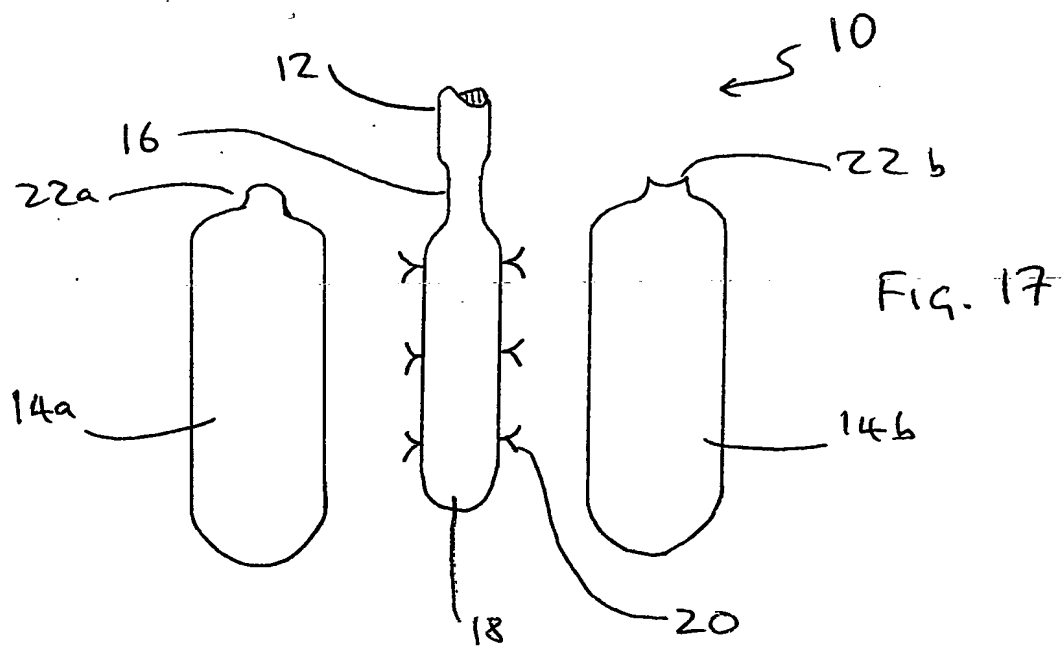
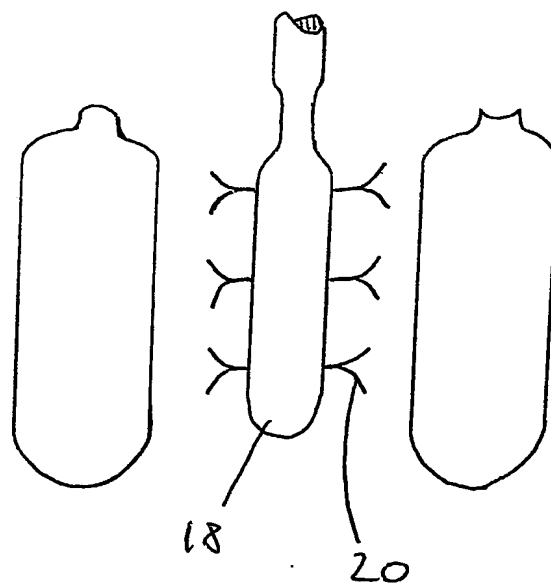
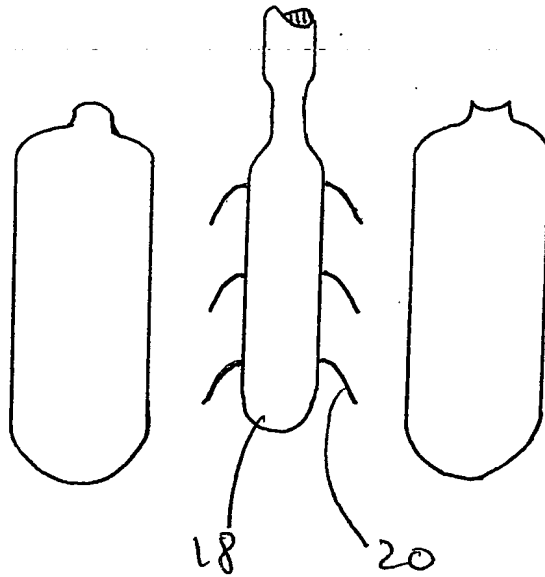


Fig. 16



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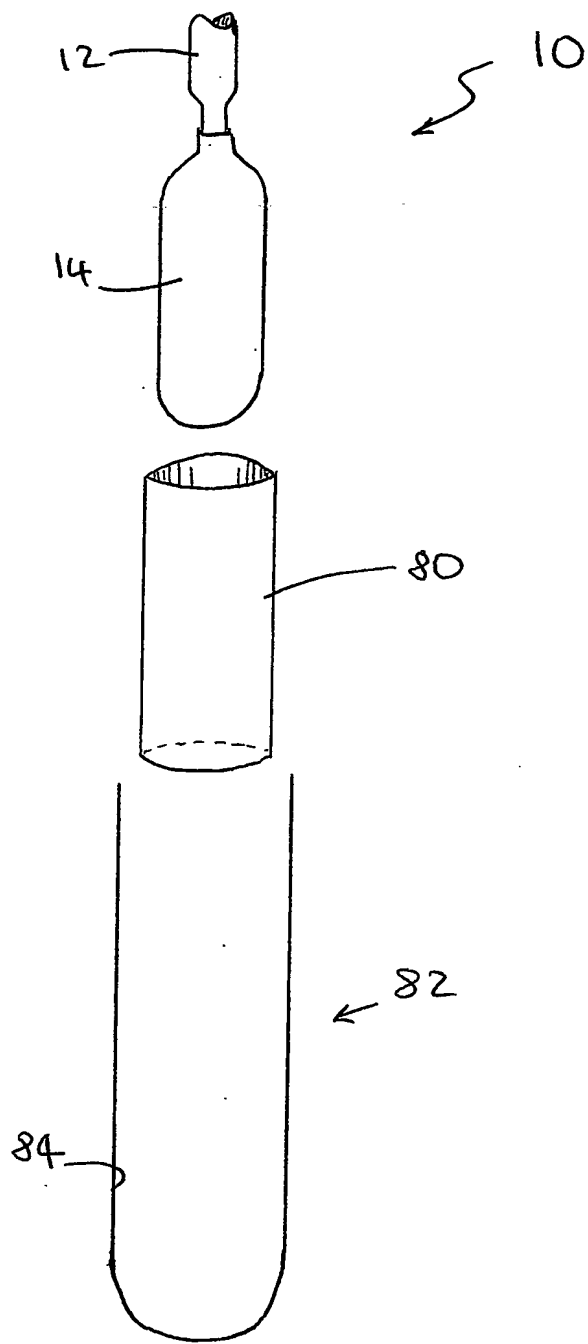


FIG. 21

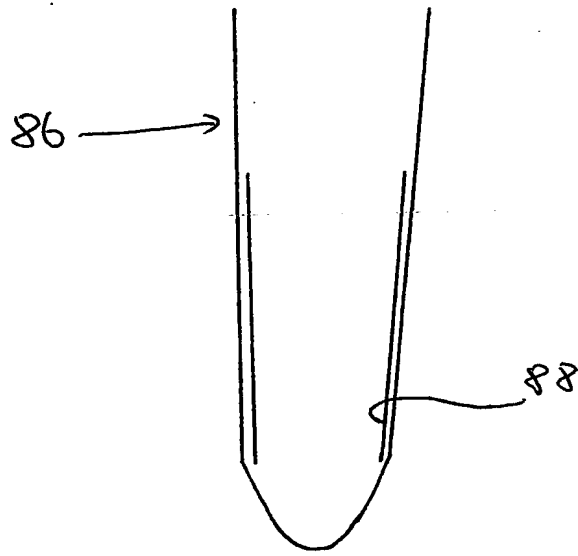


Fig. 22

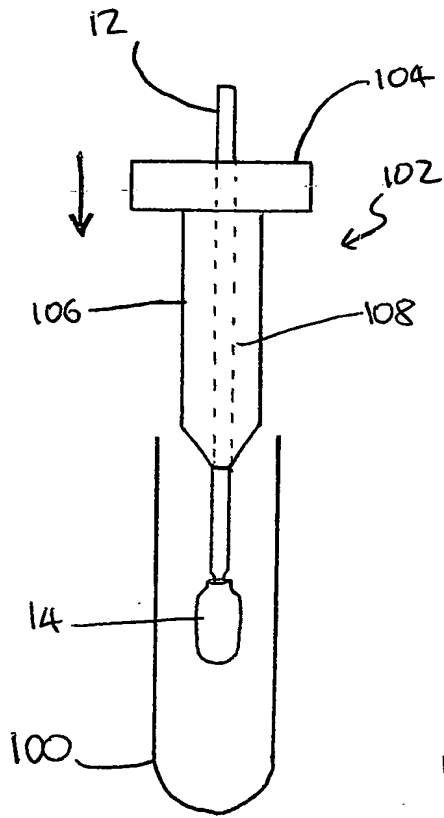


FIG. 23

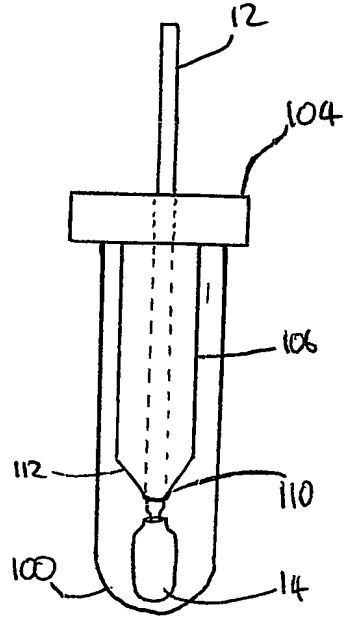


FIG. 24

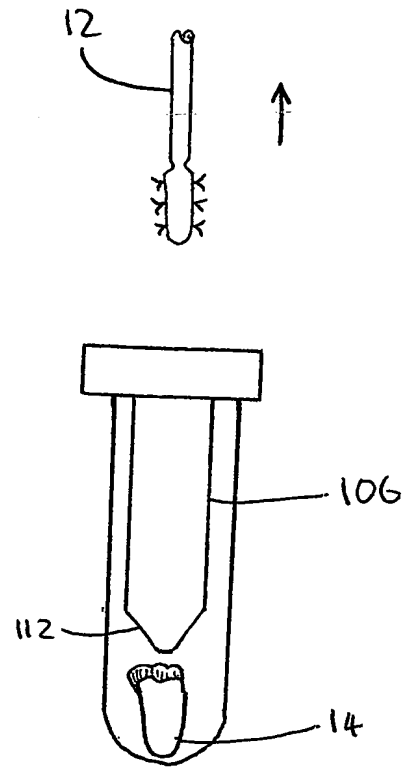


FIG. 25

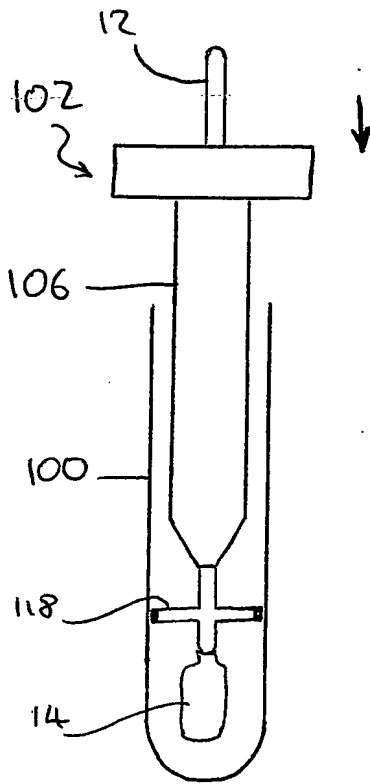


FIG. 26

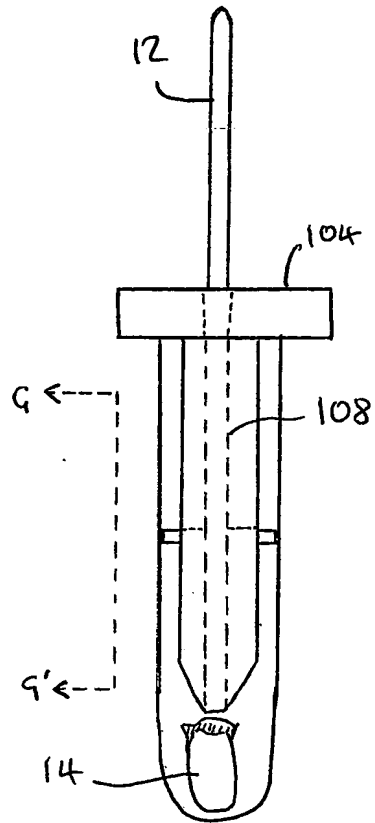


FIG. 27

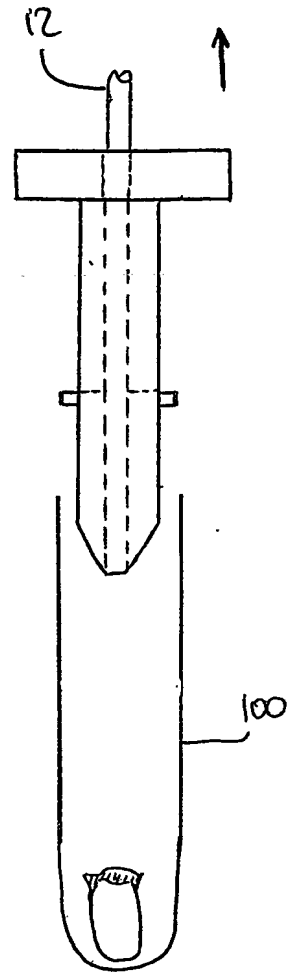


FIG. 28

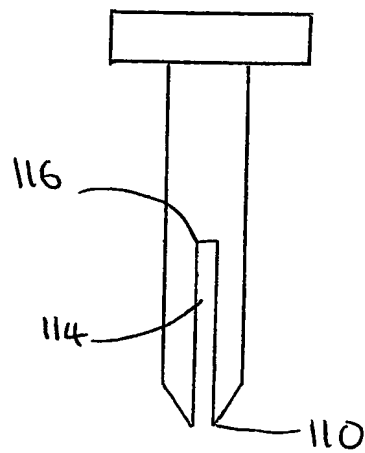


FIG. 29

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